The alveolar gas equation

By Alex Yartsev - 08/06/2015
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This chapter is most relevant to Section F9(iii) from the 2023 CICM Primary Syllabus, which expects the exam candidates to "u*nderstand respiratory equations that describe ventilation, perfusion, blood flow and respiratory mechanics".* Though there are no specific CICM primary or Fellowship exam questions which ask about this equation directly, virtually every ABG question requires the candidate to consider the A-a gradient, making the alveolar gas equation essential. In short, this equation describes the concentration of gases in the alveolus, and thus allows us to make educated guesses as to the effectiveness of gas exchange. One can use this to calculate the tension-based indices of oxygenation, such as A-a gradient or the a/A ratio (which is expressed as a percentage). The ABG machine frequently does this work for you, provided you have entered the FiO_2 and have specified that your sample is "arterial". The result is usually reported as pO_2(a/A).

The equation itself is so ubiquitous in medicine that high quality resources discussing it are common and easily available with even the laziest search strategy. The original paper ("A theoretical study of the composition of the alveolar air at altitude" by Fenn, Rahn and Otis from 1946) is, interestingly, somewhat hard to track down, and therefore worth linking to, purely out of respect. Among modern resources, the best article describing the derivation of the equation is Wang et al (2020).

The physical basis for the alveolar gas equation

The equation is necessary because there is no convenient way to sample alveolar gas. At the same time, it is gas, and therefore can be expected to behave according to some fundamental laws. Specifically, we are talking about Dalton's law, which states that

The total pressure of a mixture of gases is equal to the sum of the partial pressures of all of the constituent gases

In this scenario we can be confident that the total pressure of the mixture of gases in the alveolus is going to be basically the same as atmospheric pressure, as the alternative hypothesis would have us either explode or implode. Let us represent this total pressure as:

$$P_{atmos} = 760\ mmHg.$$

Next, the pressures of the constituent gases. Of these, some may be predictable. For example, the human body is usually at around 37 degrees, and the gas mixture is predictably humidified up to 100% humidity by its passage though the airways, such that the absolute water content of the alveolar gas mixture is predictably 44g/L. At this temperature, water vapour exerts a pressure of 47 mmHg (this, by the way, is Gay-Lussac's law). Thus, in a mixture of gases where there is 44g/m^3 of water vapour present, the water vapour will exert a partial pressure of 47 mmHg.

That leaves only 713 mmHg of partial pressure for the rest of the gases. This is because the inhaled gas mixture does not have the water vapour *added to it* like a sum, i.e. the partial pressure of the alveolar gas is not 807 mmHg (760 mmHg + 47 mmHg). Rather, the inspired gas mixture is *diluted* with the addition of water vapour until the mixture is about 6.2% water vapour and 93.8% original gas mixture. The partial pressure exerted by the remains of the original atmospheric gas mixture is therefore 713 mmHg, and the total alveolar gas mixture can now be represented as:

$$P_{atmos} + P_{H2O} = 760\ mmHg$$

Of this remaining gas mixture, the vast majority would surely have to be nitrogen and oxygen. The human body neither generates nor consumes significant amounts of atmospheric nitrogen, which means the alveolar gas should contain approximately the same amount of nitrogen as the ambient atmosphere. Thus, the nitrogen content of this 713 mmHg should be 78%, and the oxygen content should be 21%, because the Earth titrates its FiO_2 to 21% (or, more precisely, 20.9%).

Why does it do that? Thankfully, this would not be the first ridiculous digression in physiology. For instance, John F. Nunn has written a chapter

(Chapter 1 of *Nunn's Respiratory Physiology*) about the atmosphere. In it, he is grateful that greenhouse gases have allowed the existence of surface water for the last 4000 million years, and he laments that the sun "proceeds remorselessly towards becoming a red giant, which will ultimately envelop the inner planets". Unfortunately the rest of the textbook proceeds soberly along a straight and predictable path. A better introduction into the subject would probably be afforded by *The Chemical Evolution of the Atmosphere and Oceans*, by Heinrich D. Holland. The author confesses on page 2 that "the range of topics considered in the book is uncomfortably large", and that due to the mass of information "chaos was a continuous threat" during the assembly of the manuscript. In any case, for a monograph written between the years 1968 and 1981, this is a fine work. It is deserving of attention from anybody who has finished with their final CICM exams and still has some enthusiasm for the written word.

Anyway: to digress no further, let us again return to the idea that the alveolar gas mixture should contain similar proportions of oxygen and nitrogen to the atmosphere. In other words,

$$PN_2 + PO_2 = 713\ mmHg$$

Or rather,

$$PN_2 + PO_2 + P_{H2O} = 760\ mmHg$$

The partial pressure of nitrogen is never directly measured because nitrogen is boring and is of no interest to anyone, except in the context of trying to measure dead space by the Fowler method. There is about as much nitrogen in the body fluids as there is in the alveolar gas mixture, and it is neither created nor consumed. The nitrogen concentration is therefore left out of the equation. Oxygen, on the other hand, is both interesting clinically, and variable in its concentration. Assuming that there is nothing in the inspired gas mixture other than oxygen, nitrogen and water vapour, the equation that describes the concentration of oxygen in while ignoring the unknown amount of nitrogen looks like this:

$$PO_2 = FiO_2 \times (P_{atmos} - P_{H2O})$$

This gives us 149.73 mmHg as the partial pressure of oxygen, and that would be the oxygen concentration of the inspired gas mixture. However, the alveolar

gas also contains CO_2. This also needs to be incorporated into the gas equation. Like water vapour, it is incorporated into the partial pressure fractions, which means it eats into the pressures of oxygen and nitrogen equally. If one were breathing 100% FiO_2, the PCO_2 would be subtracted directly from the PO_2, i.e. a 10mmHg increase in PCO_2 would result in a 10mmg Hg decrease in PO_2. But while breathing room air, all fractions are reduced proportionally, i.e. that 10mmHg increase in PCO_2 causes a 7.9 mmHg decrease in PN_2 and a 2.1 mmHg decrease in PO_2, preserving this relationship:

$$PO_2 + P_{H2O} + PCO_2 + PN_2 = 760\ mmHg$$

Or, incorporating FiO_2, considering we do not know what the PO_2 is:

$$FiO_2 \times (P_{atmos} - P_{H2O}) + P_{H2O} + PCO_2 + PN_2 = 760\ mmHg$$

Or

$$FiO_2 \times (P_{atmos} - P_{H2O}) + PCO_2 = (760\ mmHg - PN_2 - P_{H2O})$$

If one were for whatever reason calculating the alveolar *nitrogen* equation, PN_2 here should be

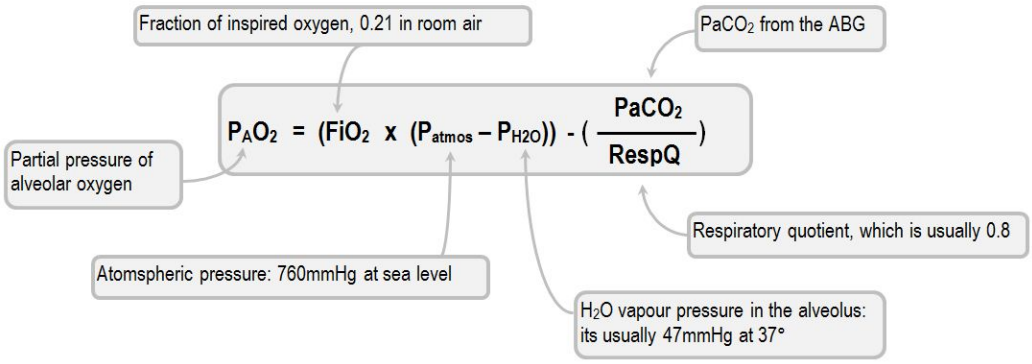
$$(1\text{-}FiO2) \times (760\ mmHg - P_{H2O})$$

But we do not care about the PN_2, and moreover we are now also bored with the water vapour, as we are mainly interested in the alveolar oxygen concentration. Fortunately we do not need to involve them because they are fairly constant and predictable. We can therefore eliminate both of them from our thinking completely, and rearrange the equation so it produces the PAO_2 as the result:

$$FiO_2 \times (P_{atmos} - P_{H2O}) - PCO_2 = PAO_2$$

This still leaves the alveolar CO_2 concentration as an unknown. It would be inconvenient to sample it from the alveolar capillary blood (with which alveolar CO_2 should be in reasonably good equilibrium), but we can sample it from the arterial blood, and introduce it into the equation with a respiratory quotient (RQ) modifier which represents the extra CO_2 that is added during the passage of arterial blood through the tissues. For most normothermic people with a conventional diet this RQ modifier is around 0.8.

This gives us the modern form of the equation:



On room air and at sea level, we can assume certain constants:

$$PAO_2 = (0.21 \times (760 - 47)) - (PaCO_2 \times 1.25)$$

Thus:

$$PAO_2 = (149 - (PaCO_2 \times 1.25)$$

Thus, the patient with a relatively normal PaCO2 (say, 40) :

$$PAO_2 = (149 - 50)$$

So, a normal person should have a PAO_2 of around 99 mmHg.

Or, for a patient with normal $PaCO_2$ and an increased FiO_2:

$$PAO_2 = (FiO2 \times 713) - 50$$

Of course, it is possible to have a strange respiratory quotient, but for this we would need to measure the total body VO_2 and VCO_2, which can only be accomplished by means of indirect calorimetry.

So, what should your PAO_2 be at any given FiO_2? In mmHg, the values are as follows:

FiO2 21%	100
FiO2 30%	164
FiO2 40%	235
FiO2 50%	307
FiO2 60%	378

FiO2 70%	449
FiO2 80%	520
FiO2 90%	592
FiO2 100%	662

In a nutshell, one can say that for every 10% increase in FiO_2, the PAO_2 will rise by about 71-72 mmHg.

Alveolar hypoventilation as the cause of hypoxia

Considering the limitations of the tension-based indices of oxygenation, the only role for the alveolar gas equation is said to be the detection of alveolar hypoventilation as the cause of hypoxia. Medical students and junior critical care trainees are captured during a highly susceptible impressionable age and indoctrinated with the idea that, while breathing room air, you can hypoventilate and accumulate so much CO_2 in the alveolar gas mixture that the Daltonian balance of partial pressures cannot contain enough O_2 to support normoxia. In other words, CO_2 displaces O_2 from the gas mixture, producing hypoxia - or so the fable reads. However, this is an inversion of the real causal relationship. The PAO_2 drops not because of Dalton's law, but because oxygen is being consumed by being incorporated into CO_2, and then the CO_2 is not being exhaled effectively (because the minute ventilation has dropped). This is beautifully expressed by a letter from David A. Story from the Alfred in Melbourne to the editor of *Anaesthesiology* (1996), which was followed by a response by John F. Nunn. Considering the value of this exchange, it is curious that the concepts these authors had outlined are not better popularised. To hopefully improve its representation, what follows is an attempt to paraphrase and expand these excellent comments.

Consider: the rate of oxygen consumption, VO_2, is described by this Fick equation:

$$VO_2 = V_A \times (FiO_2 - FAO_2)$$

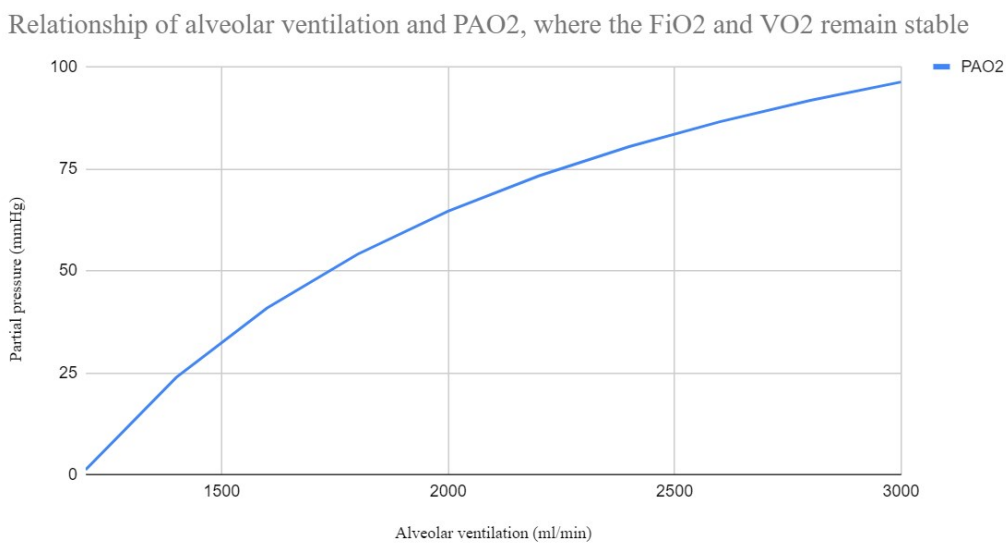
where:

V_A is alveolar ventilation

FiO_2 is the fraction of inspired O_2

FAO_2 is the fraction of alvolar (i.e. exhaled) O_2

It's not rocket science: the minute volume multiplied by the difference between the amount of inhaled oxygen and exhaled oxygen is the total oxygen consumption (and if oxygen was not being consumed, that difference would be zero). From this equation, it follows that if the VO_2 remains stable (as it does, because organs have got to keep metabolising stuff), and the FiO_2 remains stable, then then the fraction of alveolar oxygen must decrease with decreasing V_A:



It would be possible to end the explanation of hypoventilation-related hypoxia here, as by itself this is sufficient and self-evident, but we have yet to see how CO2 also increases. To elaborate, CO_2 consumption (VCO_2) is also described by a similarly straightforward equation:

$$VCO_2 = V_A \times PACO_2 / (P_{atmos} - P_{H2O})$$

where:

P_{atmos} is the total atmospheric pressure

P_{H2O} is the partial pressure of water vapour

$PACO_2$ is the partial pressure of alveolar CO_2

VCO_2 is the total CO_2 production

V_A is alveolar ventilation

Yes, the amount of CO_2 produced and exhaled per unit time is logically just the minute volume times the fractional concentration of CO^2 in the alveolar gas mixture. And you can also rearrange this to yield $PACO_2$:

$$PACO_2 = (P_{atmos} - P_{H2O}) \times (FiCO_2 + VCO_2 / V_A)$$

The $FiCO_2$ usually being zero,

$$PACO_2 = 713 \times (VCO_2 / V_A)$$

The bottom line is that the alveolar ventilation is an essential component of calculating both VO_2 and VCO_2. Why is this interesting? Well: VO_2 and VCO_2 are interrelated: for every unit of oxygen consumed, a certain amount of CO2 is produced. This relationship is represented as the respiratory quotient (RQ):

$$RQ = VCO_2 / VO_2$$

where:

VCO_2 is CO_2 production

VO_2 is O_2 consumption

This means that the rates of oxygen consumption CO_2 production and alveolar ventilation are all inextricably linked. For example, if you make the RQ equation all about VCO_2,

$$VCO_2 = RQ \times VO_2$$

you can then represent the VCO_2 using the Fick relationship mentioned above, and produce an equation that contains all three variables:

$$V_A \times PACO_2 / (P_{atmos} - P_{H2O}) = RQ \times VO_2$$

This means you cannot alter the V_A without changing the VCO_2 and the VO_2 in opposite directions, to a magnitude proportional to the RQ. Observe what happens when we plug some standard variables into this equation:

$$2852 \times 50 / (760-47) = 0.8 \times 250,$$

where

V_A= 2852 ml/min

VO_2 = 250 ml/min

RQ = 0.8

P_{H2O} = 47 mmHg

If VCO_2 obeys the rules, it should be 200 ml/min (because $VCO_2 = RQ \times VO_2$)

Thus, $PACO_2 = 713 \times (VCO_2 / V_A)$ = 50 mmHg

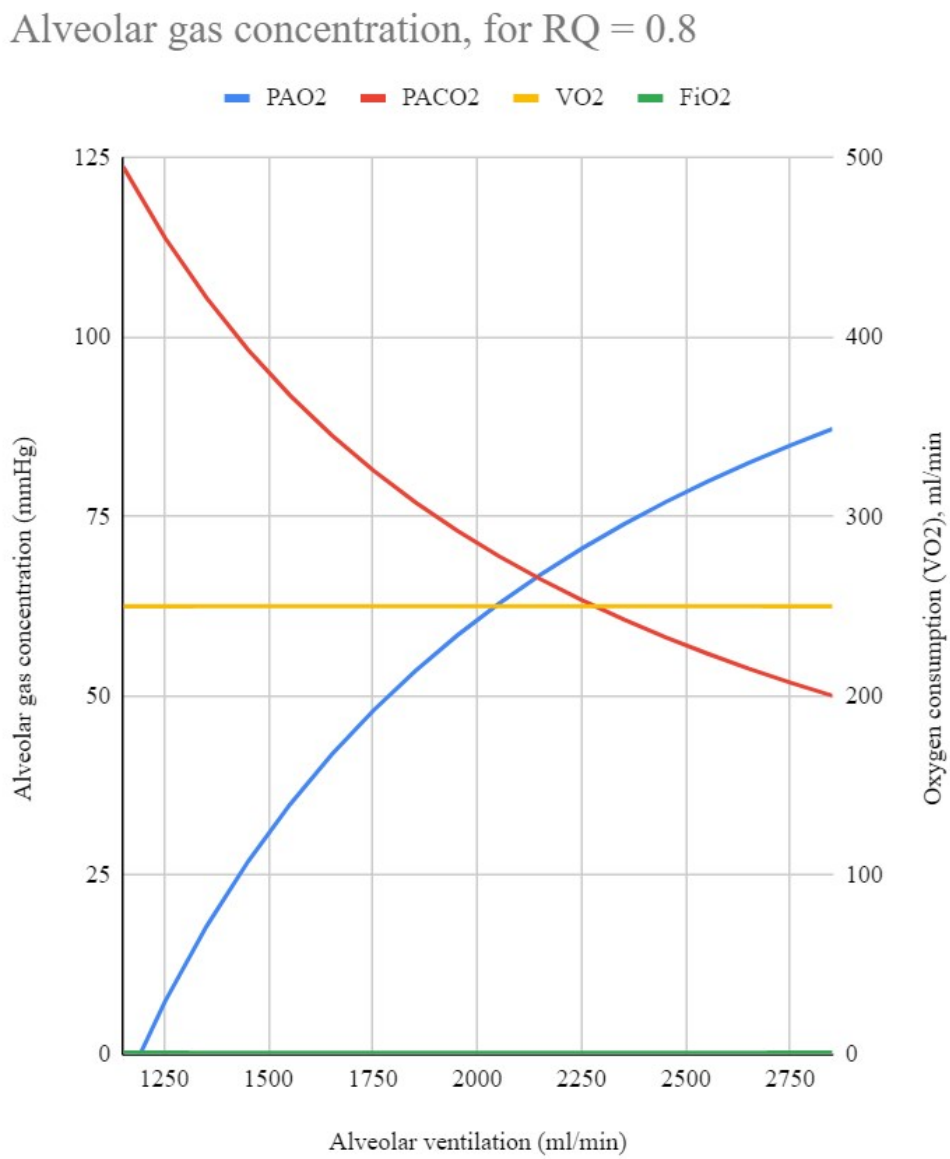
These numbers would then give us a PAO_2 of 87.23 mmHg if they were plugged into Nunn's universal air equation, which describes the relationship of PAO_2 to alveolar ventilation oxygen consumption and barometric pressure:

$$PAO_2 = (P_{atmos} - P_{H2O}) \times (FiO_2 - VO_2 / V_A)$$

$$= 713 \times (0.21 - 250/2852)$$

$$= 87.23\ mmHg$$

And, plugging these equations into a spreadsheet, we can produce a totally unrealistic graph that tracks the relationship of PAO_2 and $PACO_2$ for a respiratory quotient of 0.8, all the way down to a completely ludicrous PAO_2 of 0 mmHg:



Yes, these gas mixtures do happen to obey Dalton's law, but that is probably because *they all do.* The point is that Dalton's law is not the reason the PAO_2 is dropping here.

To summarise:

- With the oxygen consumption remaining the same, CO_2 production by the tissues remains stable.
- With decreasing alveolar ventilation, CO_2 removal from the alveolus *decreases*, which means the $PACO_2$ increases.
- If the FiO_2 remains the same, a larger fraction of the FiO_2 ends up being removed from the alveolus to satisfy the stable delivery of oxygen, and the fraction of oxygen in the alveolus decreases, according to the equation

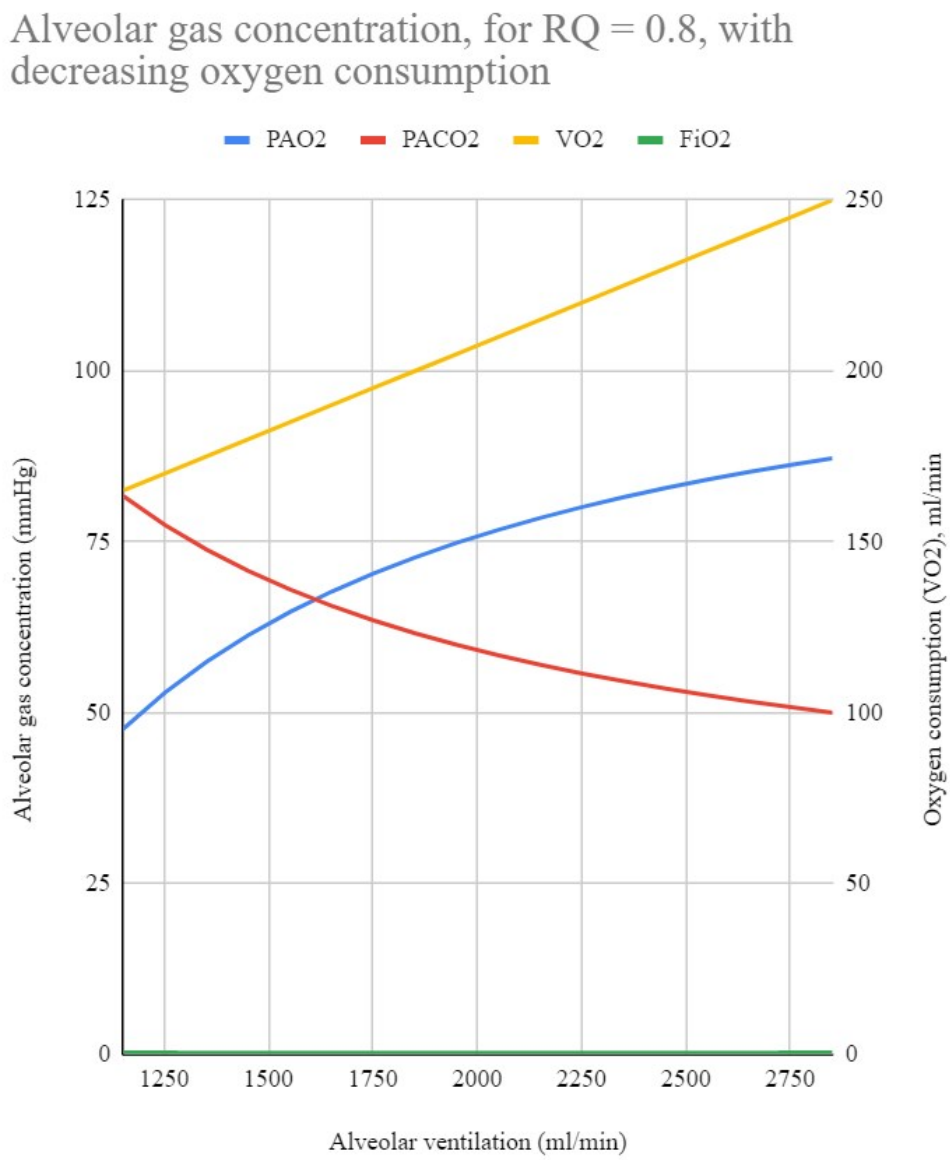
$$VO_2 = V_A \times (FiO_2 - FAO_2)$$

- The rate of these changes in response to changes in alveolar ventilation is a function of the respiratory quotient.
- The total mixture of gases remains obedient to Dalton's Law, where the total pressure of the mixture of gases remains equal to the sum of the partial pressures of all of the constituent gases.

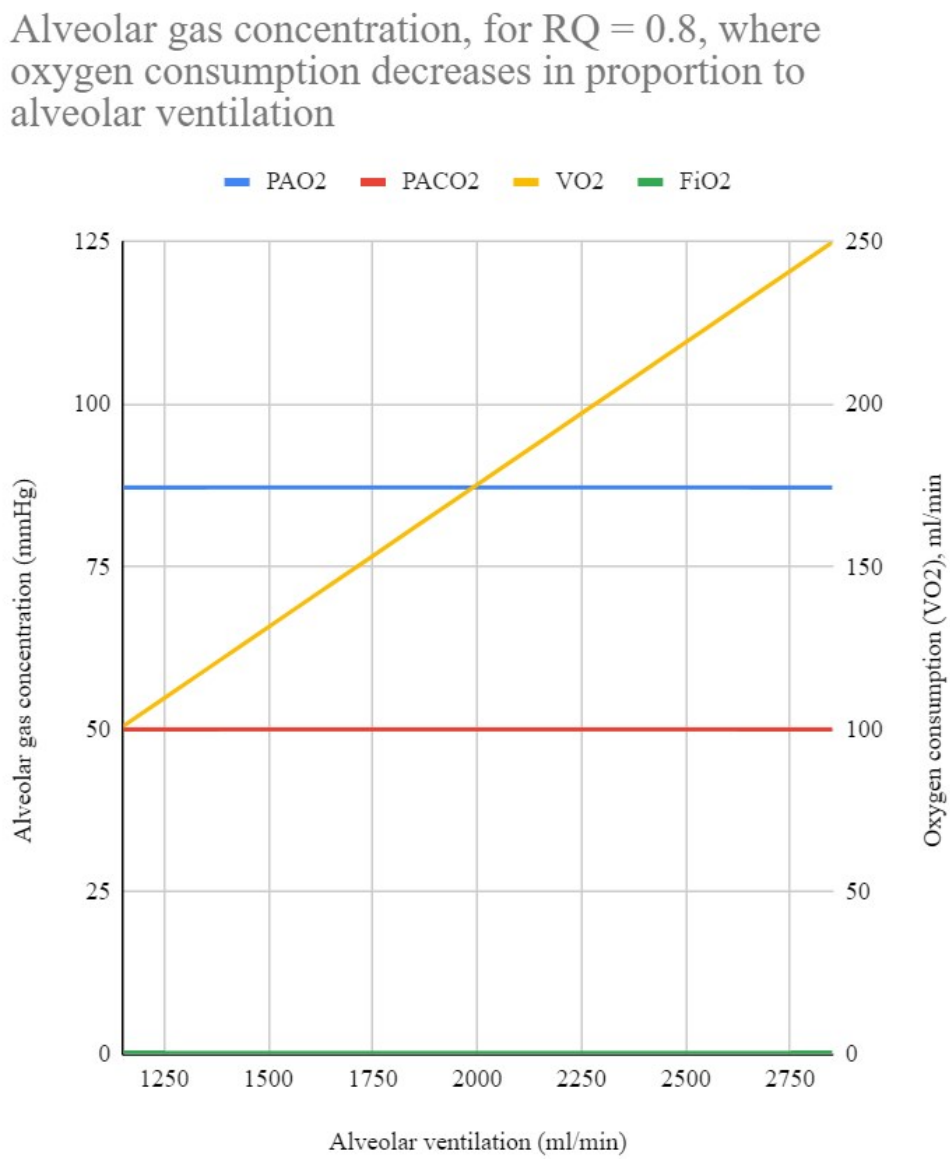
Can anyone be hypoxic due to hypoventilation when the $PaCO_2$ is normal?

The respiratory quotient relationship suggests that it should be impossible to hypoventilate yourself down into blue hypoxia without becoming hypercapnic in the process; but occasionally some readers may observe something different clinically, and they should be grateful to a contributor (Professor Shyam Kothari) for bringing this conundrum into the open.

Perhaps you can just lay there and produce less CO_2 through lowering your metabolism? Starting with the premise that CO_2 production is the necessary consequence of O_2 consumption, we assume that the only way you can produce little CO_2 is to consume little oxygen. But if you consume little oxygen, then you only extract a small amount of oxygen from the alveolar gas (Nunn's universal air equation gives us the relationship of PAO_2 to alveolar ventilation and oxygen consumption). So with changing VO_2, the relationship between $PACO_2$ and PAO_2 will remain the same, i.e. they will still change in opposite directions, albeit more gradually. Observe, a hypothetical anaesthetic drops the alveolar ventilation at the same time as it decreases oxygen consumption:



From this, it follows that one might be able to find a rate of change at which the rate of VO2 decrease can match the rate of decreasing alveolar ventilation; i.e. where VO_2 decreases in proportion to the decrease in V_A, logically one should expect the alveolar gases to remain stable:



But this does not achieve the desired endpoints, as we are looking for a scenario where the patient has to be hypoxic, hypoventilating, *and* with a normal CO_2. In this fashion we are giving the equation a series of fixed variables. Let's agree on how hypoxic we want this hypothetical patient to be:

- $PACO_2$ = 40 mmHg, as we agree that it will remain normal, and
- PAO_2 = 50 mmHg, as we agree that it will be low, for sats in the 80s.
- VO_2 = 250 ml/min, as we agree that we will not meddle with it.
- V_A = low, but let's keep it as the x-axis for consistency

Using the equation from above, we can plug these values in:

$$V_A \times 40 / (P_{atmos} - P_{H2O}) = RQ \times 250$$

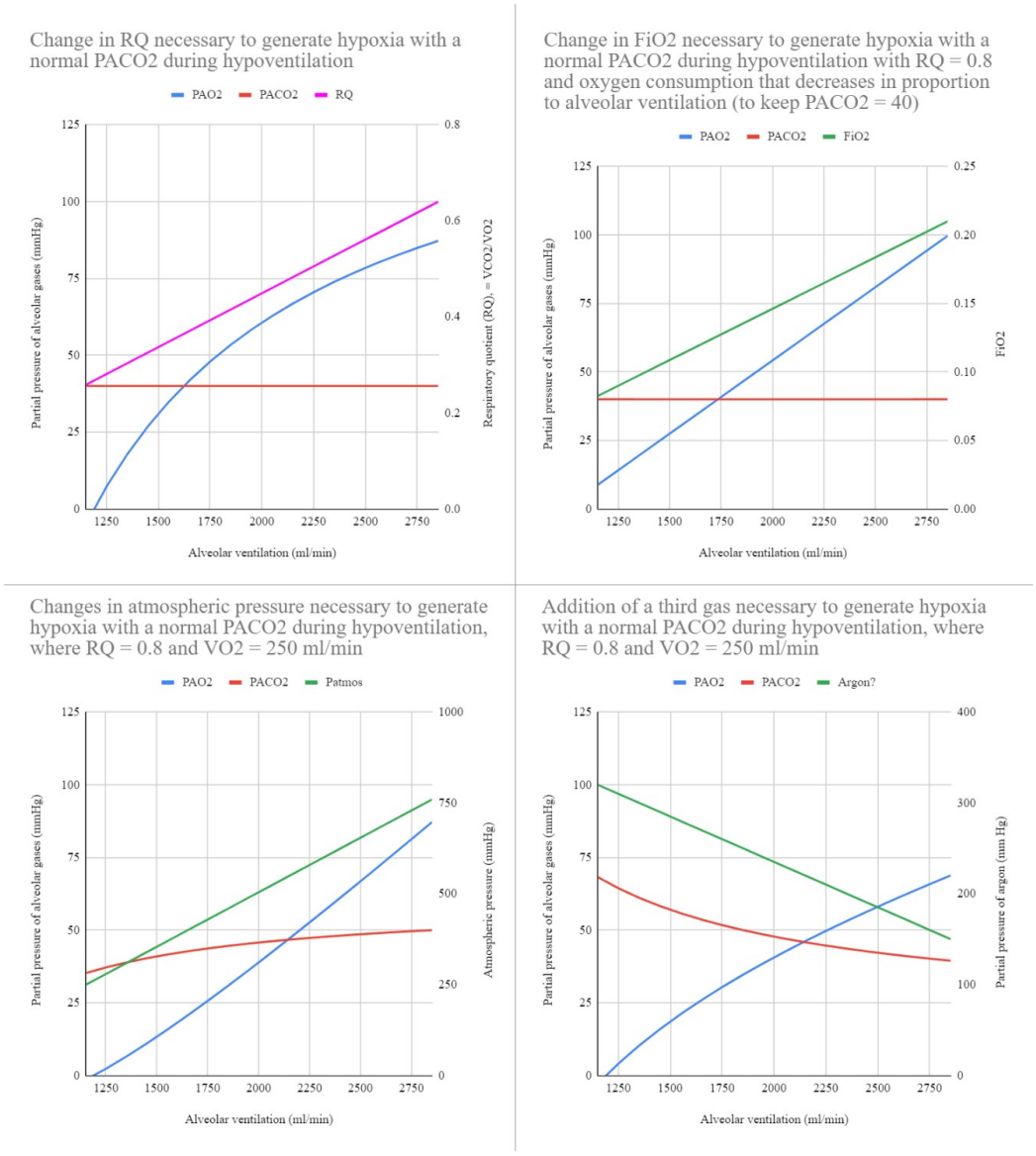
So, the remaining variables are RQ, P_{atm}, and FiO_2. Solving for these variables:

$$RQ = (V_A \times PACO_2 / (P_{atmos} - P_{H2O})) / VO_2$$

$$FiO_2 = PAO_2 / (P_{atmos} - P_{H2O}) + VO_2 / V_A$$

$$P_{atmos} = PAO_2 / (FiO_2 - VO_2 / V_A) + P_{H2O}$$

Graphing the results generates a series of nightmarishly unphysiological scenarios which produce the desired set of results at the expense of the reader's sanity:



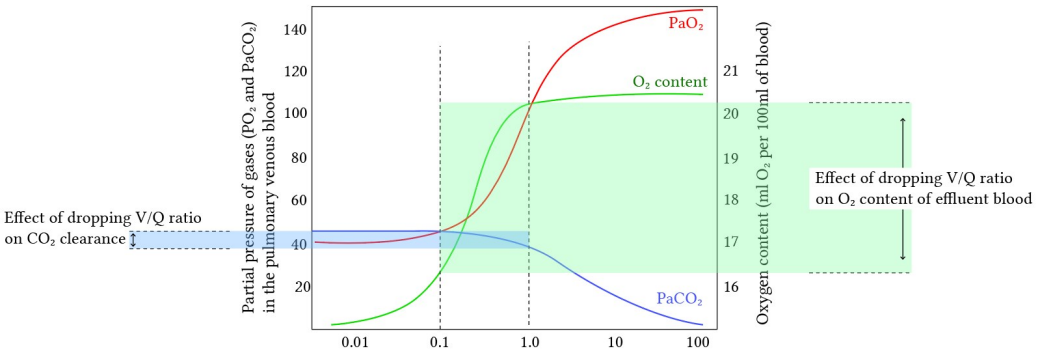
Before they succumb to critical psychic damage, the reader is reminded that these pointless thought experiments are *intended* to be ridiculous, and that nobody is suggesting that the $PACO_2$ will actually remain near normal when the PAO_2 is zero due to low atmospheric pressure. The main point is that CO_2

is tied to O_2 consumption and it is impossible to cheat this relationship within the range of physiological performance characteristics of the human organism. To generate this situation, one would have to have an extremely low CO_2 production relative to O_2 consumption, and this could only be due to:

- A bizarrely low RQ ratio
- An unaccounted-for loss of oxygen
- An unaccounted-for loss of CO_2

Even where there is an extreme reliance on fat metabolism (as there is less CO2 produced relative to O2 consumed during the oxidation of fatty acids), an RQ below 0.6 would be truly ridiculous. As an example, extreme ketosis can trend in the direction of 0.67, cardiac arrest survivors are occasionally observed to have RQs in the ~0.6 range because they are probably wasting their oxygen for nonmetabolic things (eg. free radical generation), but anything below this would be insane. For example, an RQ of 0.4 would mean that 60% of all the oxygen ends up being used by some mysterious process (is the patient combusting, decomposing, or feeding a giant population of microorganisms?) Bacteria and yeast can go this low, and an RQ of ~ 0.4 were measured during one experiment in fermentation by Slavov et al (2014), but it would be unexpected among eukaryotes.

More than likely, the observation of hypoventilation, hypoxia and normocapnia in a patient is the consequence of VQ scatter. Consider this memorable diagram from West (1977):



The reason for bringing this up is to remind us that a change in VQ ratio has a significant effect on oxygenation, but a modest effect on CO_2 clearance. As such, it should be possible to have enough VQ scatter to create hypoxia

without creating hypercapnia, provided enough of one's lung units had VQ ratios in the ~0.1 range. This is completely plausible in the context of, for example, atelectasis during sedation (where the patient is hypoventilating enough to collapse the bases of their lungs and become hypoxic, but is not sedated enough to become hypercapnic from respiratory depression).

Previous chapter: Common respiratory equations

Next chapter: Oxygen tension - based indices of oxygenation

References

The Alveolar Gas Equation was first described in a famous work by Wallace Fenn, Hermann Rahn, and Arthur Otis.

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